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10/590,940	09/26/2006	Domenico Geraci	GRT/4161-18	1415

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,940	GERACI, DOMENICO	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28 and 33-48* is/are pending in the application.

4a) Of the above claim(s) *33-36 and 40-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28 and 37-39 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 10/20/2010 is acknowledged.

2. Claims 23-28 and 33-48 are pending.

3. Claims 33-36 and 40-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/29/2009.

4. Claims 23-28, 37-39 and 44-48 are currently under examination as they read on a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens, pharmaceutical compositions thereof and methods of preparing a pharmaceutical composition.

5. Applicant's IDS document filed on 10/20/2010 has been considered.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 23-28, 37-39 and 44-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-33 of copending Application No. 10/557,586 in view of Columbo et al.(IDS filed on 10/20/2010) and Columbo et al. (IDS filed 08/28/2006).

Claims 29-33 of U.S. Application 10/557,586 are directed to Parj1/Parj2 multimer proteins comprising mutations. In particular, a multimer protein molecule comprising amino acid sequences SEQ ID NO:4 and SEQ ID NO:2 for medical use as a hypoallergenic agent and a pharmaceutical composition comprising an effective amount of the multimer protein molecule and suitable adjuvants.

The claimed invention differs from the prior art in the recitation of "said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen" of claim 26; and "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27.

Columbo et al. (IDS filed on 10/20/2010) teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and

60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, page 2781-2782 'Materials and Methods', sequences in Figures 2-3, whole document). Columbo et al. teaches that mutation of positions C4, C14, C29, and C30 effects structure and substitution with serine at positions 14 and 29 and deletion of position 29 leads to a decrease in IgE binding in this region (In particular, page 2782 first full paragraph, Figure 2). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

Columbo et al. (IDS filed on 08/28/2006)teaches that the Par j 1 major allergen has been shown to adopt the same structural fold with four disulfide bridges in the following order: Cys4-Cys52, Cys14-Cys29, Cys30-Cys75 and Cys50-Cys91and that the same folding has been shown for Par j 2; The immunodominant IgE epitope is located in the loop l region located between alpha-helixl and alpha-helix2 in the region from amino acids 1 to 30 (In particular, Table 2, page

177). The reference teaches that Cys14-Cys29, Cys30-Cys75 are the cysteine bridges that are most important for IgE binding and allergenicity (In particular, page 177, right column).

It would have been obvious to one of ordinary skill in the art at the time of invention to mutate the multimer protein of U.S. Application Number 10/557,586 at the cysteine residues 4, 29 and 30 in both Par j1 and Parj 2 portions to decrease IgE binding for in vivo pharmaceutical use.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 23-28, 37-39 and 44-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 26-27, 45 and 47-48 recites amino acid residues by number without a reference sequence, making the claims indefinite. Without the inclusion of a SEQ ID NO to the

claims, amino acids numbers reads on any amino acids, particularly since the claims are directed to fusion proteins which may comprise any deletion and any number of amino acids from any other protein added anywhere to the protein.

Correction is required.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 23-28, 37-39 and 44-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: the fusion protein of SEQ ID NO:4 and a composition thereof, the specification does not provide reasonable enablement for: **a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens** of claim 23; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge** of claim 24; characterized in that it **comprises allergens Parjl and Parj2 of the Parietaria judaica species** of claim 25; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in**

positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen of claim 26; **characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52** of claim 27; a **pharmaceutical composition** comprising **the fusion protein** according to claim 25 and a pharmaceutically acceptable excipient of claim 37; **a fusion protein characterized in that it comprises the amino acid sequences of the different allergens Parjl and $Parj_{2,}$ belonging to the non-specific Lipid Transfer Protein (ns-LTPs)family from Parietariajudaica species, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one selected from the group consisting of 4-52, 14-29, and 30-75 disulphide bridges and in that said sequences maintain essentially the same length as the sequences of wild type allergens** of claim 45; **characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge** of claim 46; **characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 52 and 75 of the amino acid sequence of Parjl and/or Parj2 allergen** of claim 47; and **characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gin or Leu residues in**

positions 29 and 30 or 4, 29 and 30 or 29, 30 and 52 and as applied to claims 38 and 44 for the same reasons as set forth in the Office Action mailed on 04/15/2010.

Applicant's arguments filed on 10/20/2010 have been fully considered, but are not found persuasive

Applicant argues:

> "Claims 23-27, 37-39 and 44 were rejected under Section 112, first paragraph, because the specification allegedly does not reasonably provide enablement for the full scope of the claimed invention. Applicants traverse because the teachings in their specification enable the skilled artisan to practice their invention as presently claimed.
>
> The Examiner contends that the disclosure of Parj1 and Parj2 allergens, along with the working example of making the amino acid sequence of SEQ ID NO: 4, is not sufficient to teach a skilled artisan to practice the claimed invention without undue experimentation. Applicants disagree because the working examples are merely illustrative of their invention and do not limit the practice thereof. Here, the knowledge of other proteins in the non-specific Lipid Transfer Protein (ns-LTPs) family, the high level of skill in the art to prepare fusion proteins lacking one or more of the four disulphide bridges present in the wild type sequences, and Applicants' teachings in the present specification are clearly sufficient to enable the full scope of the claimed invention.
>
> Withdrawal of the enablement rejection is requested because it would not require undue experimentation for a skilled artisan to make and use the claimed invention. "

It is the Examiner's position that the Office Action mailed on 04/15/2010 provided numerous references detailing the unpredictability in making and using the genus of fusion proteins encompassed by the instant claims.

The specification only discloses the generation of the fusion protein of SEQ ID NO:4. The specification has not adequately disclosed the genus of fusion proteins comprising "the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present

in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens." The specification has only disclosed Par j 1 and Par j 2, which does not provide sufficient basis for the recitation of any "non-specific lipid transfer protein." In addition, the disclosure of "Par j 1" and "Par j 2" is not sufficient basis for all Par j 1 and Par j 2 proteins, having any variations from wild type, as encompassed by the recitation of "Par j 1" and "Par j 2" proteins.

The specification also does not adequately disclose a fusion protein comprising additional sequences added onto the N-and/or C-terminus and having any number of undisclosed mutations. Without guidance in the specification as to what areas to avoid making mutation and/or guidance regarding how to make mutations in designated areas, the resulting mutated polypeptides will have unpredictable activities and binding properties.

Further, there is no predictability that the fusion proteins disclosed will have pharmaceutical use. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the protein as a pharmaceutical composition as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed composition is effective for in vivo use to treat allergy, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

The generic disclosure of fusion proteins comprising allergens having mutations is not enabled. The specification provides no testable function that would allow one of ordinary skill in the art to be able to determine whether or not to determine what is or is not a fusion protein encompassed by the instant claims that can be used for the disclosed diagnostic and therapeutic functions. As such, the rejection is maintained.

12. Claims 23-28, 37-39 and 44-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: the fusion protein of SEQ ID NO:4 and a composition thereof.

Applicant is not in possession of: **a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens** of claim 23; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge** of claim 24; characterized in that it

comprises allergens Parjl and Parj2 of the Parietaria judaica species of claim 25; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen** of claim 26; **characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52** of claim 27; a **pharmaceutical composition** comprising **the fusion protein** according to claim 25 and a pharmaceutically acceptable excipient of claim 37; **a fusion protein characterized in that it comprises the amino acid sequences of the different allergens Parjl and $Parj_{2,}$ belonging to the non-specific Lipid Transfer Protein (ns-LTPs)family from Parietariajudaica species, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one selected from the group consisting of 4-52, 14-29, and 30-75 disulphide bridges and in that said sequences maintain essentially the same length as the sequences of wild type allergens** of claim 45; **characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge** of claim 46; **characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 52 and 75 of the amino acid sequence of Parjl and/or Parj2 allergen** of claim 47; and **characterized in that it contains amino acid**

sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gin or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30 and 52 and as applied to claims 38 and 44 for the same reasons as set forth in the Office Action mailed on 04/15/2010.

Applicant's arguments filed on 10/20/2010 have been fully considered, but are not found persuasive.

Applicant argues:

> "Claims 23-27, 37-39 and 44 were rejected under Section 112, first paragraph, because they contain subject matter that allegedly was not described in the specification in such a way as to .reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse because they disclose a representative number of species within the claimed genus. The guidance that the Examiner alleges would be required, but is absent from this specification, would have been known to a person skilled in the art at the time this application was filed. A specification need not teach, and preferably omits, what is well known in the art. See Hybritech v. Monoclonal Antibodies, 231 USPQ 81, 94 (Fed. Cir. 1986).
>
> As explained above, the disclosure of other proteins in the non-specific Lipid Transfer Protein (ns-LTPs) family, the manufacture of a fusion protein lacking one or more of the four disulphide bridges present in the wild type sequence, and Applicants' teachings in the present specification are clearly sufficient to establish that the claimed invention has been adequately described.
>
> Withdrawal of the written description rejection is requested because the specification conveys to a skilled artisan that Applicants were in possession of the claimed invention as of the filing date.

Applicant has disclosed the fusion protein of SEQ ID NO:4; "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" Ex parte Kubin (83 U.S.P.Q.2d 1410 (BPAI 2007)), at page 16. In this instant case, Applicants have not provided any guidance as to structure of the genus of recited fusion proteins s that will possess the activity of being able to used pharmaceutically. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" supra, at page 17. In the instant case,

definition by function does not suffice to define the genus because it is only an indication of what the fusion does, rather than what it is.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 23-28, 37-39 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Columbo et al. (IDS filed on 10/20/2010) in view of Columbo et al. (IDS filed on 08/28/2006) Bonura et al. (IDS filed on 08/28/2006) and Pauli et al. (PTO-892 mailed on 04/15/2010; Reference U).

Columbo et al. (IDS filed on 10/20/2010) teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, page 2781-2782

'Materials and Methods', sequences in Figures 2-3, whole document). Columbo et al. teaches that mutation of positions C4, C14, C29, and C30 effects structure and substitution with serine at positions 14 and 29 and deletion of position 29 leads to a decrease in IgE binding in this region (In particular, page 2782 first full paragraph, Figure 2). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

The claimed invention differs from the prior art in the recitation of "a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that it comprises allergens Parjl and Parj2 of the Parietaria judaica species" of claim 25; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of

the amino acid sequence of Parj 1 and/or Parj2 allergen" of claim 26; "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, Ile, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27 and "comprising the amino acid sequence SEQ ID NO: 4" of claim 36; "a pharmaceutical composition comprising the fusion protein according to claim 25 and a pharmaceutically acceptable excipient" of claim 37; "the pharmaceutical composition according to claim 37 in the form of a solution, suspension, emulsion, cream, ointment or implant" of claim 38; and :a method for preparation of the pharmaceutical composition according to claim 37, the method comprising mixing said protein in an immunologically active amount with a pharmaceutically acceptable excipient of claim 44."

Columbo et al. (IDS filed on 08/28/2006)teaches that the Par j 1 major allergen has been shown to adopt the same structural fold with four disulfide bridges in the following order: Cys4-Cys52, Cys14-Cys29, Cys30-Cys75 and Cys50-Cys91and that the same folding has been shown for Par j 2; The immunodominant IgE epitope is located in the loop 1 region located between alpha-helixl and alpha-helix2 in the region from amino acids 1 to 30 (In particular, Table 2, page 177). The reference teaches that Cys14-Cys29, Cys30-Cys75 are the cysteine bridges that are most important for IgE binding and allergenicity (In particular, page 177, right column).

Bonura et al. teaches that Par j 1 is a major allergen in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29,

C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

Pauli et al. teaches that dimer and trimer multimer fusion proteins of Bet v 1 in pharmaceutical compositions exhibited reduced skin reactions as determined by in vivo intradermal and skin prick testing (In particular, whole document). The reference also teaches that the dimer and trimer fusion Bet v 1 molecules had retained IgE binding capacity and fold, but microaggregation led to decreased effector cell activation (In particular, page 1081, second full paragraph). The reference suggested that pharmaceutical compositions comprising the multimers for the treatment of allergy should also contain adjuvants to prevent spreading of molecules and to decrease systemic reactions (In particular, page 1082, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of both Columbo et al. references and Pauli et al. produce a multimer fusion protein comprising Par j 1 and Par j 2 to treat allergies because Par j 1 and Par j 2 are the major allergens of Parietaria pollen. It would have been obvious to only include these two allergens since they are the two major allergens and it is desirable to produce pharmaceutical

compositions which only comprise the most important allergens without the confounding effects of the seven minor allergens and other components normally present in pollen allergen extracts. By combining Par j 1 and Par j 2 into a single molecule, the molar ratio of the two allergens will be constant, thus providing a controlled dosage of both allergens to patients for optimal immunotherapy use. Because Pauli et al. teaches that dimerization and trimerization of allergens does not lead to a change in the conformation of the allergen fold and Columbo et al. teaches that the 1-30 IgE epitope of Par j1 and Par j 2 is a conformational, discontinuous epitope, it would also have been obvious to perform mutational analysis at the positions taught by Columbo et al. to generate a Par j1/ Par j2 multimer protein with reduced IgE binding at that epitope. One would be motivated to do this because Columbo et al teaches that it is an important IgE epitope and because the multimer is being generated for in vivo use. It is obvious to combine two compositions which are known to have the same use. One of ordinary skill in the art at the time of invention would have been motivated to perform mutations to arrive at SEQ ID NO 4 for in vivo allergy therapy use, which may further contain an adjuvant because such a molecule would be expected to exhibit reduced IgE binding in addition to reduced effector cell activation when used in vivo to treat allergies. It would be obvious to one of ordinary skill in the art at the time the invention was made to combine the compositions of Columbo et al. and Pauli et al. because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 10/20/2010 have been fully considered, but are not found persuasive.

Applicant argues:

> "..Colombo also does not disclose, or even make obvious, that the disruption of disulphide bridges is the sole means to inhibit IgE binding. Instead, a range of possible mutations including cysteine, lysine (K), and glutamic acid (E) residues are disclosed. Further, Colombo does not teach or make obvious any specific combination of modifications, such as the combination C4, C29 and C30 characterizing the fusion protein PjEDcys (see Fig. 2 and SEQ ID NO:4). Rather, Colombo teaches away from constructs comprising modification in positions C30 or C4 because pPj1.5 (C30) and pPJ17 (C4) are still capable of bindinq IqE. Finally, Colombo fails to teach or make obvious any dimeric fusion protein that comprises muteins of two different allergens (e.g., Parjl and Parj2). This difference was acknowledged by the Examiner.
>
> Bonura corresponds to the disclosure of WO 02/20790 and teaches muteins of only the Parjl allergen. The IgE binding activity of any single mutein PjA, PjB, PjC and PjD is analyzed, and the results are the same as those reported in Fig. 9 of the present application at issue. Bonura, like Colombo, does not teach or make obvious any hetero-dimer fusion protein comprising muteins of two different allergens, namely Parjl and Parj2.
>
> The Examiner asserts, however, that Pauli teaches the improved efficacy of a dimeric form of an allergen and would, therefore, suggest the construction of a dimeric fusion protein comprising the Parjl and Parj2 allergens as mutated according to Colombo or Bonura. This conclusion is clearly wrong.
>
> Firstly, Pauli's experimental work relates to Bet v-1 allergen and its derivatives. But Bet v-1 and Bet v-2 are birch (betullaceous) tree pollen allergens that are taxonomically not related to the plants and ns-LTP allergens of Applicants' invention. Pauli's disclosure appears to be completely immaterial as regards the claimed invention, since the results reported therein does not suggest anything concerning the activity of a group of allergens (ns-LTP) totally unrelated to birch tree allergens. There is also no other evidence of record establishing a reasonable expectation of success that one of ordinary skill in the art would have predicted the effects obtained when the modifications reported by Pauli are applied to ns-LTP allergens, nor would the same inhibition of IgE binding observed by Pauli be expected for a totally different allergen group.

> Further, Pauli discloses derivatives (i.e., either fragments or dimers or trimers) of a single allergen: Bet v 1. Thus, one of ordinary skill in the art, by combining Pauli with Colombo and Bonura, would have prepared, at best, an allergen derivative, perhaps in modified form, free of one or more disulphide bridges, but always deriving from only one allergen: either Parjl or Parj2. Therefore, even combining the three cited documents together, one of ordinary skill in the art would not have concluded from the evidence of record that it was obvious to prepare a heterodimeric fusion protein comprising different allergens, such as both Parjl and Parj2.
>
> Finally, Pauli not only does not make obvious the claimed invention, but actually teaches away from preparing and assaying any dimeric fusion protein. One of ordinary skill in the art is cautioned of the risk of anaphylactic side effects induced by injecting Bet v-1 wild type allergen or a derivative thereof (see page 1082, right hand column, middle paragraph, starting with "That hypoallergenic molecules can be injected..."). For this reason, Pauli specifically admits, "We did not include Bet vl dimer in the intra- dermal tests because it proved to have a higher skin test reactivity than Bet vl trimer in the skin pick test" (page 1082, left hand column, last paragraph). For this reason, Pauli concludes, "It is planned to prepare vaccine which consist of the two rBet v-1 fragments or rBet v-1 trimer adsorbed to AI(OH)3" (page 1082, last line, et seq.). Therefore, one of ordinary skill in the art reading Pauli would not have found it obvious to prepare a fusion
> protein comprising a Bet v-1 dimer.
>
> In other words, Pauli's disclosure would have dissuaded - rather than motivated - one of ordinary skill in the art from preparing and assaying any dimeric fusion protein as claimed herein, specifically in the present claims 23 and 28.

It is the Examiner's position that the fact that Bet v 1 is from birch tree pollen instead of a P. judaica plant pollen does not make the art of Pauli et al. non-applicable. Bet v 1, Par j 1 and Par j 2 are all allergens and that is what makes the combination of the references appropriate. It is the Examiner's position that the combination of the references provides more than ample motivation to mutate every combination and permutation of the cysteine residues in the 1-30 region of Par j1 and Par j2. The allergens are highly homologous in the 1-30 region of both proteins and the Columbo references teach that antibodies crossreact with both proteins in this region due to homologous IgE binding epitopes. Therefore, the argument that Pauli doesn't provide motivation to put Par j 1 and Par j 2 in a multimer is not persuasive. The art recognizes their similarity. In addition, the reasons to put them both in a multimer are cited supra.

The Columbo references and Bonura reference together provide motivation to change the conformational IgE binding epitopes of Par j 1 and Par j 2. The references highlight the important residues for structure and IgE binding. It is obvious to mutate and/or delete one or more of the cysteine residues involved in the maintaining structure and IgE binding. One would have a high expectation of success in generating hypoallergenic molecules. There were mutants that exhibited increased IgE binding. The expectation of success need only be reasonable to generate the fusions.

15. Claims 23-28, 37-39 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (PTO-892 mailed on 04/15/2010; Reference V) in view of Colombo (IDS filed on 08/28/2006), Columbo et al. (IDS filed on 10/20/2010) and Bonura et al. (IDS filed on 08/28/2006)

Vrtala et al. teaches recombinant multimeric protein allergen such as dimer and trimer of major birch pollen allergen Bet vl, (In particular, page 2045 and whole document). The recombinant trimer consisting of three covalently linked copies of the allergens is useful for inducing IgG antibodies in vivo (pharmaceutical composition mixed in solution, comprising pharmaceuticaly acceptable excipient) and blocking IgE binding to Bet vl and related allergens, (In particular, abstract and page 2047).

The claimed invention differs from the prior art in the recitation of " a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in

the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that it comprises allergens Parjl and Parj2 of the Parietaria judaica species" of claim 25; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parj 1 and/or Parj2 allergen" of claim 26; "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27 and "comprising the amino acid sequence SEQ ID NO: 4" of claim 36.

Columbo et al. (IDS filed on 10/20/2010) teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of

SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, page 2781-2782 'Materials and Methods', sequences in Figures 2-3, whole document). Columbo et al. teaches that mutation of positions C4, C14, C29, and C30 effects structure and substitution with serine at positions 14 and 29 and deletion of position 29 leads to a decrease in IgE binding in this region (In particular, page 2782 first full paragraph, Figure 2). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

Columbo et al. (IDS filed on 08/28/2006)teaches that the Par j 1 major allergen has been shown to adopt the same structural fold with four disulfide bridges in the following order: Cys4-Cys52, Cys14-Cys29, Cys30-Cys75 and Cys50-Cys91and that the same folding has been shown for Par j 2; The immunodominant IgE epitope is located in the loop l region located between alpha-helixl and alpha-helix2 in the region from amino acids 1 to 30 (In particular, Table 2, page 177). The reference teaches that Cys14-Cys29, Cys30-Cys75 are the cysteine bridges that are most important for IgE binding and allergenicity (In particular, page 177, right column).

Bonura et al. teaches that Par j 1 is a major allergens in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of

SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29, C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Par j 1 and Par j2 allergens taught by the Colombo references and Bonura et al. in the major birch pollen allergen Bet vl dimers and trimers of Vrtala et al because Vrtala et al. teaches that the dimers and trimers are useful for diagnosis and/or treating allergy. Both Colombo et al. references teache that Par j1 and Pa j 2 can themselves be useful for diagnosis and therapy of Parietaria pollen allergy, so it would be obvious to generated multimer fusions of the allergens for diagnosis and therapy as well. It would have been obvious to mutate both Par j 1 and Par j 2 in the same cysteine residues since Columbo et al. (IDS filed 10/20/2010) teaches that Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the

invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 10/20/2010 have been fully considered, but are not found persuasive.

Applicant argues:

> "Vrtala's disclosure is not substantially different from Pauli. Vrtala relates to Bet v- 1 allergen. As already explained above, Bet v-1 is a birch tree (betullaceous) pollen allergen and is not related to the ns-LTP allergens of the present application. The cited document appears to be completely immaterial as regards the claimed invention, since the results reported therein does not suggest anything concerning the activity of a group of allergens (ns-LTP) totally unrelated to birch tree allergens. There is also no other evidence of record establishing a reasonable expectation of success that one of ordinary skill in the art would have predicted the effects obtained when the modifications reported by Vrtala are applied to ns-LTP allergens, nor would the same inhibition of IgE binding observed by Vrtala be expected for a totally different allergen group.
>
> Further, Vrtala discloses dimers or trimers of a single allergen: Bet v 1. Thus, one of ordinary skill in the art, by combining Vrtala with Colombo and Bonura, would have prepared, at best, an allergen derivative, perhaps in modified form, free of one or more disulphide bridges, but always deriving from one allergen: either Parjl or Parj2. Therefore, even combining the three cited documents together, one of ordinary skill in the art would not have concluded from the evidence of record that it was obvious to prepare a heterodimeric fusion protein comprising different allergens, such as both Parjl and Parj2.
>
> In any case, Vrtala, like Pauli, focuses on a trimer rather than a dimer of Bet vl allergen. This is evident not only from the title, but also from the section "Conclusions" that are totally silent on any reason to prepare the dimer. The reason resides in the fact that the dimer is much less preferred than the trimer for use because the former induces a higher skin reaction and allergic activity when compared to the latter. This is shown in the results reported in section "Recombinant Bet vl trimer exhibits profoundly reduced allergic activity" on page 2045. The mean wheal diameters of the skin reaction area (at 10 IJg/ml) is 4.1 + 2.4 (dimer) vs. 0.7 + 1.2 (trimer) and (at 100 IJg/ml) 7.3 + 2.5 (dimer) vs. 3.6 + 2.1 (trimer). These results confirm the previously discussed prior art's teaching away from Applicants' invention, and would have further contributed to dissuading one of ordinary skill in the art from considering the dimeric form as a valid tool for preparing a vaccine for immunotherapy. "

It is the Examiner's position that the fact that Bet v 1 is from birch tree pollen instead of a P. judaica plant pollen does not make the art of Vrtala non-applicable. Bet v 1, Par j 1 and Par j

2 are all allergens and that is what makes the combination of the references appropriate. It is the Examiner's position that the combination of the references provides more than ample motivation to mutate every combination and permutation of the cysteine residues in the 1-30 region of Par j1 and Par j2. The allergens are highly homologous in the 1-30 region of both proteins and the Columbo references teach that antibodies crossreact with both proteins in this region due to homologous IgE binding epitopes. Therefore, the argument that Vrtala doesn't provide motivation to put Par j 1 and Par j 2 in a multimer is not persuasive. The art recognizes their similarity. In addition, the reasons to put them both in a multimer are cited supra. Vrtala does not teach away from making a dimer. The trimer was particularly hypoallergenic. That does not mean that one would not be motivated to make a dimer, particularly in the is instance where two different allergens are being used in the dimer and for reasons stated supra with respect to relative dosage.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 3, 2011

/Nora M Rooney/

Primary Examiner, Art Unit 1644